REMARKS

Claims 1-44 and 49 are pending. Claims 1-11 and 20-23 are under consideration. Claims 12-19, 24-44 and 49-51 are withdrawn.

The claims are presented in accordance with the revised amendment practice.

In response to the objection to claims 6-9 and 20, Claim 6 is editorially revised to reintroduce "1" after "claim" to provide proper dependency. This language was in claim 6 as amended in the Preliminary Amendment submitted December 31, 2001. Claim 20 is amended to depend from claim 1. Reconsideration and withdrawal of the objection are respectfully requested.

In response to the rejection of claim 20 under 35 U.S.C. § 101, applicants amend claim 20 to obviate any basis for the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

The Office Action rejects claims 1-11 and 20-23 under 35 U.S.C. § 112, first paragraph. In particular, the Office Action asserts:

> The specification fails to overcome unpredictability of promoter activity as set forth by the art so as to provide the guidance necessary for one of skill in the art to use the claimed nucleic acid comprising any promoter capable of driving expression of human Tau in the nervous system of a non-human animal...
>
> There is insufficient guidance in the specification, in view of the state of the art at the time of filing, to determine that broadly claimed nucleic acid would have the claimed effect of preventing endogenous Tau expression and cause Tau-hyperphosphorylation in the broad number of animal species encompassed by the claims. There is also insufficient guidance in the specification to overcome the underdeveloped nature of the art of ES cell technology to enable one of skill in the art to make and use the totipotent cells encompassed by the claims.

Office Action at pages 6 and 8.

In response, Applicants submit that the specification provides ample guidance to those skilled in the art to use the claimed nucleic acid with a promoter to drive the expression of human Tau in the nervous system of a non-human animal. The specification discloses:

> The sequence capable of directing expression of said human Tau protein or the modulator thereof is preferably a transcriptional control sequence which can steer expression of the proteins to the nervous system of the

> non-human animal. Transcriptional control sequences according to the invention comprise a suitable promoter and other regulatory regions, such as enhancer sequences, that can modulate the activity of the promoter.
>
> Regulatory elements required for the expression include promoter sequences to bind RNA polymerase and transcription initiation sequences for ribosome binding. For example, a bacterial expression vector may include a promoter such as the lac promoter and for transcription initiation in the Shine-Dalgarno sequence an the start codon AUG. Similarly, a eukaryotic expression vector may include a heterologous or homologous promoter for RNA polymerase II, a downstream polyadenlylation signal, the start codon AUG, and a termination codon for detachment of the ribosome. **Such vectors may be obtained commercially or assembled from the sequences described by methods well known in the art**...
>
> **DNA sequences that drive expression to neurons are known. They include both control systems that are neuron-specific and control systems that are more or less promiscusous but that induce high levels of expression in neurons.** Depending on the nature of the construct used in the production of the transgenic animal and, in particular, the control elements, the desired proteins may be expressed in all neurons of transgenic animals. **Neuron-specific control systems, that drive expression to neuronal cell types in general, are known. They may be derived from genes encoding neuron-specific proteins.** Such systems may be used to bring about expression of the desired Tau protein and/or the protein capable of [its] modulation, in neurons.
>
> Preferably the sequence is a promoter which directs expression of said proteins in the neurons of the brain or other such cells including astrocytes, oligodendrocytes microglia of Schwann cells. Preferably, the promoter is the mouse Thy-1 promoter which drives expression in mouse central neurons.

Specification at pages 5-6. Applicants submit that this disclosure coupled with what was known in the art at the time this application was filed provides sufficient guidance to one skilled in the art how to drive expression of human Tau in the nervous system of a non-human animal.

Applicants also submit that the specification provides ample guidance to those skilled in the art that the claimed nucleic acid would have the claimed effect of preventing endogenous Tau expression and cause Tau-hyperphosphorylation in the

broad number of animal species encompassed by the claims. For example, the specification discloses:

> **Incorporation of the nucleic acid sequences into the vector according to the invention for subsequent transformation and integration into the genome of said host cell or non-human animal is carried out by procedures well known to those skilled in the art as provided in Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbour Laboratory Press.** The vector may be introduced by transfection or other suitable techniques such as electroporation. In the present invention, the incorporation of the exogenous DNA into the genome of the animal is accomplished by electroporation of the vector in embryonic stem cells. The cells that have the exogenous DNA incorporated into their genome by homologous recombination may subsequently be injected into blastocytes for generation of the transgenic animals with the desired phenotype. Successfully transformed cells which contain the vector according to the invention may be identified by well known techniques, such as lysing the cells and examining the DNA by, for example, Southern blotting or using the polymerase chain reaction.

Specification at pages 9-10.

> **Antisense technology can be used to control gene expression through triple-helix formation of antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA.** For example, the 5' coding portion of the mature protein sequence, which encodes for the protein of the present invention, is used to design an antisense RNA oligonucleotide of from 10 to 50 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple-helix – see Lee et al. Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241:456 (1988); and Dervan et al., Science, 251: 1360 (1991), thereby preventing transcription and the production of human Tau or the protein capable of modulating Tau according to the invention defined herein. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of an mRNA molecule (antisense – Okano, J. Neurochem., 56:560 (1991); Oligodeoxynucleotides and Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)).

Specification at page 12. See also, specification at pages 12-13.

There is also sufficient guidance in the specification to permit one skilled in the art to apply ES cell technology to make and use the cells encompassed by the claims. See, e.g., pages 17-18.

Reconsideration and withdrawal of the rejection of claims 1-11 and 20-23 under 35 U.S.C. §112, first paragraph, are respectfully requested.

In response to the rejection of claims 1-11 and 22under 35 U.S.C. § 112, second paragraph, applicants amend claims 1 and 22 to obviate any basis for the rejections Reconsideration and withdrawal of the rejection are respectfully requested.

Early consideration and prompt allowance of the pending claims is respectfully requested.

Respectfully submitted,

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